#### PATENT

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (Case No. 01-1145-A)

In the App	plication of:	)
	Boyle et al.	) Examiner: Blanchard
Serial No.	10/408,901	)
Filed:	April 7, 2003	) Group Art Unit: 1645
	man Anti-OPGL Neutralizing Antibodies Selective OPGL Pathway Inhibitors	) Confirmation No.: 6128
Mail Ston	Amendment	

Mail Stop: Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

# AMENDMENT AND RESPONSE TO OFFICE ACTION, MAILED SEPTEMBER 10, 2008

Dear Sir

Please consider the following amendments and remarks made in response to the Office Action mailed September 10, 2008. Applicants submit herewith a three month extension of time and a supplemental information disclosure statement (IDS), along with the associated fees upon filing. Accordingly, a response is timely filed on or before March 10, 2009

No other fees are believed due; however if any other fee is due, the Commissioner is authorized to charge such fee to our deposit account 13-2490.

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Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 15 of this paper.

## Amendments to the Claims

The following listing of claims replaces all prior versions of the claims:

(Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain comprises a heavy chain variable region comprises comprising any of SEQ ID NO: 6 SEQ ID NO: 14, SEQ ID NO: 22, or SEQ ID NO: 26, or wherein the antigen-binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 6 SEQ ID NO: 14, SEQ ID NO: 22, or SEQ ID NO: 26.

## (Canceled)

3. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain variable region and a light chain variable region, wherein the heavy-chain comprises a heavy chain variable region comprises comprising any of SEQ ID NO: 10 or SEQ ID NO: 18, or wherein the antigen-binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 10 or SEQ ID NO: 18.

## 4. (Canceled)

# 5. (Canceled)

6. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain variable region and a light chain variable region, wherein the light chain comprises a light chain variable region comprises emprising any of SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 24, or SEQ ID NO: 28, or wherein the antigen binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 24, or SEQ ID NO: 28.

# 7. (Canceled)

8. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain variable region and a light chain variable region, wherein the light chain comprises a light chain variable region comprises comprising any of SEQ ID NO: 12 or SEQ ID NO: 20, or wherein the antigen binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO:12 or SEQ ID NO:20.

# (Canceled)

- 10. (Canceled)
- 11. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises any of SEQ ID NO: 30, SEQ ID NO: 38, SEQ ID NO: 46, or SEQ ID NO: 50-or wherein the antigen-binding fragment comprises at least CDR1, CDR2, and CDR 3 of SEQ ID NO: 6, SEQ ID NO: 14, SEQ ID NO: 22, or SEQ ID NO: 26.

# 12. (Canceled)

13. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises a SEQ ID NO: 34 or SEQ ID NO: 42, or wherein the antigen binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 10 or SEO ID NO: 18.

## (Canceled)

- (Canceled)
- (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and

a light chain, wherein the light chain comprises any of SEQ ID NO: 32, SEQ ID NO: 40, SEQ ID NO: 48, or SEQ ID NO: 52, or wherein the antigen binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 24, or SEQ ID NO: 28

- (Currently Amended) The antibody of any of claims 1, 6, 11, orelaim 16, wherein the antibody specifically binds the D-E loop region of human osteoprotegerin ligand (OPGL).
- 18. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the light chain comprises SEQ ID NO: 36 or SEQ ID NO: 44,—or wherein the antigen binding fragment comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 12 or SEO ID NO: 20.
- (Currently Amended) The antibody of any of claims 3, 8, 13, orelaim 18, wherein the antibody specifically binds to:
  - a region of human osteoprotegerin ligand (OPGL) that is outside the D-E loop region; or
  - both a region of human OPGL that is outside the D-E loop region and all or a
    portion of the D-E loop region.
- 20. (Previously Presented) The antibody of claim 19, wherein binding to both a region of human OPGL that is outside the D-E loop region and all or a portion of the D-E loop region is consecutive or simultaneous.

## (Canceled)

- (Previously Presented) The antibody of any of claims 23, 25, 27, 29, 31, 32,
   or 34, wherein the antibody specifically binds the D-E loop region of human osteoprotegerin ligand (OPGL).
- 23. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 6 and the light chain comprises a light chain variable region comprising SEQ ID NO: 8, or wherein the antigen-binding fragment thereof of the heavy chain variable region comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 6 or and CDR1, CDR2, and CDR3 of SEQ ID NO: 8.

## (Canceled)

25. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 14 and the light chain comprises a light chain variable region comprising SEQ ID NO: 16, or wherein antigen-binding fragment thereof comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 14 erand CDR1, CDR2, and CDR3 of SEQ ID NO: 16.

# 26. (Canceled)

27. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 22 and the light chain comprises a light chain variable region comprising SEQ ID NO: 24, or wherein the antigen-binding fragment thereof comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 22 or and CDR1, CDR2, and CDR3 of SEQ ID NO: 24.

## 28. (Canceled)

29. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 26 and the light chain comprises a light chain variable region comprising SEQ ID NO: 28, or wherein the antigen-binding fragment thereof comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 26 or and CDR1, CDR2, and CDR3 of SEO ID NO: 28.

#### (Canceled)

- 31. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 30 and the light chain comprises SEQ ID NO: 32, or wherein the antigen-binding fragment thereof comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 6 er-and CDR1, CDR2, and CDR3 of SEQ ID NO: 8.
- 32. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 38 and the light chain comprises SEQ ID NO: 40, or wherein the antigen-binding fragment thereof comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 14 or and CDR1, CDR2, and CDR3 of SEQ ID NO: 16.
- 33. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 46 and the light chain comprises SEQ ID NO: 48, or wherein the antigen-binding fragment

thereof comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 22 of and CDR1, CDR2, and CDR3 of SEO ID NO: 24.

34. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 50 and the light chain comprises SEQ ID NO: 52, or wherein the antigen-binding fragment thereof comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 26 or and CDR1, CDR2, and CDR3 of SEO ID NO: 28.

#### (Canceled)

- 36. (Previously Presented) The antibody of any of claims 38, 40, 42, or 43, wherein the antibody specifically binds to:
  - a. a region of human osteoprotegerin ligand (OPGL) that is outside the D-E loop region; or
  - b. both a region of human OPGL that is outside the D-E loop region and all or a
    portion of the D-E loop region.
- 37. (Previously Presented) The antibody of claim 36, wherein binding to both a region of OPGL that is outside the D-E loop region and all or a portion of the D-E loop region is consecutive or simultaneous.
- 38. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 10 and the light chain comprises a light chain variable region comprising SEQ ID NO: 12, or wherein the antigen-binding fragment thereof

comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 10 or-and CDR1, CDR2, and CDR3 of SEO ID NO: 12.

### (Canceled)

40. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 18 and the light chain comprises a light chain variable region comprising SEQ ID NO: 20, or wherein the antigen-binding fragment thereof comprises at least CDR1, CDR2, and CDR3 of SEQ ID NO: 18 of and CDR1, CDR2, and CDR3 of SEQ ID NO: 20.

## 41. (Canceled)

- 42. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 34 and the light chain comprises SEQ ID NO: 36, or wherein the antigen-binding fragment <a href="https://docs.org/10.15">https://docs.org/10.15</a> and CDR3 of SEQ ID NO: 10 or and CDR1, CDR2, and CDR3 of SEQ ID NO: 10 or and CDR3.
- 43. (Currently Amended) An isolated antibody or an antigen-binding fragment thereof, that specifically binds human osteoprotegerin ligand (OPGL), wherein the antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 42 and the light chain comprises SEQ ID NO: 44, or wherein the antigen-binding fragment thereof comprises at-least CDR1, CDR2, and CDR3 of SEQ ID NO: 18 or and CDR1, CDR2, and CDR3 of SEQ ID NO: 20.

- 44. (Currently Amended) The antibody or antigen-binding fragment thereof of any of claims 23, 25, 27, 29, 31, 32, 33, 34, 38, 40, 42, or 43, 59, or 65, wherein the heavy chain and light chain are connected by a flexible linker to form a single-chain antibody.
- (Currently Amended) The antibody or antigen-binding fragment thereof of claim 44, which is a single-chain Fv antibody.
- 46. (Currently Amended) The antibody-antigen-binding fragment of any of claims 23, 25, 27, 29, 31, 32, 33, 34, 38, 40, 42, or 43, 59, or 65, which is a Fab antibody fragment.
- 47. (Currently Amended) The antibody-antigen-binding fragment of any of claims 23, 25, 27, 29, 31, 32, 33, 34, 38, 40, 42, or 43, 59, or 65, which is Fab' antibody fragment.
- 48. (Currently Amended) The antibody antigen-binding fragment of any of claims 23, 25, 27, 29, 31, 32, 33, 34, 38, 40, 42, or 43, 59, or 65, which is a (Fab')<sub>2</sub> antibody fragment.
- (Canceled)
- 50. (Currently Amended) The antibody or antigen-binding fragment thereof of any of claims 23, 25, 27, 29, 31, 32, 33, 34, 38, 40, 42, or 43, 59, or 65, wherein the antibody or antigen-binding fragment thereof inhibits binding of OPGL to an osteoclast differentiation and activation receptor (ODAR).
- 51. (Canceled)
- (Currently Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment thereof of claim 50.

- 53. (Canceled)
- (Canceled)
- 55. (Canceled)
- 56. (Canceled)
- 57. (Canceled)
- 58. (Canceled)
- (Currently Amended) An isolated antibody or antigen-binding fragment thereof comprising:
- a. human heavy chain framework regions, a human heavy chain CDR1 region, a human heavy chain CDR2 region, and a human heavy chain CDR3 region; and
- b. human light chain framework regions, a human light chain CDR1 region, a human light chain CDR2 region, and a human light chain CDR3 region;

# wherein,

- the CDR1, CDR2, and CDR3 regions of the heavy chain are from of SEQ ID NO: 6, and the CDR1, CDR2, and CDR3 regions of the light chain are from of SEQ ID NO: 8;
- (ii) the CDR1, CDR2, and CDR3 regions of the heavy chain are from of SEQ ID NO: 14, and the CDR1, CDR2, and CDR3 regions of the light chain are from of SEO ID NO: 16;
- (iii) the-CDR1, CDR2, and CDR3 regions of the light chain are from of SEQ ID NO: 22, and the-CDR1, CDR2, and CDR3 regions of the light chain are from of SEQ ID NO: 24; or
- (iv) the CDR1, CDR2, and CDR3 regions of the light chain are from of SEQ ID NO: 26, and the CDR1, CDR2, and CDR3 regions of the light chain are from of SEQ ID NO: 28;

wherein the antibody or antigen-binding fragment thereof specifically binds to human osteoprotegerin ligand (OPGL).

- (Currently Amended) The antibody or antigen-binding fragment thereof of claim 59, wherein the antibody or antigen-binding fragment thereof specifically binds the D-E loop region of human osteoprotegerin ligand (OPGL).
- 61. (Canceled)
- 62. (Canceled)
- (Canceled)
- 64. (Canceled)
- 65. (Currently Amended) An isolated antibody or antigen-binding fragment thereof comprising:
  - a. human heavy chain framework regions, a human heavy chain CDR1 region, a human heavy chain CDR2 region, and a human heavy chain CDR3 region; and
  - human light chain framework regions, a human light chain CDR1 region, a human light chain CDR2 region, and a human light chain CDR3 region;

## wherein-

- the CDR1, CDR2, and CDR3 of regions of the heavy chain are from SEQ ID NO: 10, the and CDR1, CDR2, and CDR3 of regions of the light chain are from SEQ ID NO: 12; or
- (ii) the CDR1, CDR2, and CDR3 of regions of the heavy chain are from SEQ ID NO: 18, the and CDR1, CDR2, and CDR3 of regions of the light chain are from SEQ ID NO: 20;

wherein the antibody or antigen-binding fragment thereof specifically binds to human osteoprotegerin ligand (OPGL).

- 66. (Currently Amended) The antibody or antigen-binding fragment thereof of claim 65, wherein the antibody or antigen-binding fragment thereof specifically binds to:
  - a region of human osteoprotegerin ligand (OPGL) that is outside the D-E loop region; or
  - d. both a region of human OPGL that is outside the D-E loop region and all or a
    portion of the D-E loop region, wherein binding is consecutive or
    simultaneous
- 67. (Currently Amended) The antibody or antigen-binding fragment thereof of claim 66, wherein binding to both a region of human OPGL that is outside the D-E loop region and all or a portion of the D-E loop region is consecutive or simultaneous.

## 68. - 75. (Canceled)

- 76. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 6, and the light chain comprises a light chain variable region comprising SEQ ID NO: 8.
- 77. (Currently Amended) An isolated antibody that specifically binds human esteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises—a heavy chain variable region comprising SEQ ID NO: 14, and the light chain comprises—a light chain variable region comprising SEQ ID NO: 16.
- 78. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises—a heavy chain variable region comprising SEQ ID NO: 22, and the light chain comprises—a light chain variable region comprising SEQ ID NO: 24.

- 79. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises—a heavy chain variable region comprising SEQ ID NO: 26, and the light chain comprises—a light chain variable region comprising SEQ ID NO: 28.
- 80. (Currently Amended) An isolated antibody that specifically binds human esteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises—a heavy chain variable region comprising SEQ ID NO: 10, and the light chain comprises—a light chain variable region comprising SEQ ID NO: 12.
- 81. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising SEQ ID NO: 18, and the light chain comprises a light chain variable region comprising SEQ ID NO: 20.
- 82. (Currently Amended) An isolated antibody that specifically binds human esteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 30, and the light chain comprises SEQ ID NO: 32.
- (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 34, and the light chain comprises SEQ ID NO: 36.
- 84. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEO ID NO: 38, and the light chain comprises SEO ID NO: 40.

- 85. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 42, and the light chain comprises SEQ ID NO: 44.
- 86. (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEQ ID NO: 46, and the light chain comprises SEQ ID NO: 48.
- (Currently Amended) An isolated antibody that specifically binds human osteoprotegerin ligand (OPGL), comprising a heavy chain and a light chain, wherein the heavy chain comprises SEO ID NO: 50, and the light chain comprises SEO ID NO: 52.

## Remarks

# 1. Status and Support

Claims 1-20, 22, 23, 25, 27, 29, 31-34, 36-38, 40, 42-48, 50, 52, 59, 60, 62, 64-67, and 76-87 are currently pending; claims 21, 24, 26, 28, 30, 35, 39, 41, 49, 51, 53-58, 61, 63, and 68-75 are canceled. Applicants have amended claims as noted above. Support for the claim amendments can be found in the original claims and throughout the specification including, for example, Figures 15 & 16; page 16, lines 1-20; the Examples (see, e.g., Example 3 and Table 4); the Summary of the Invention (pp. 2-11); and the original claims. No new matter has been introduced as a result of these amendments.

The above amendments to the claims are made without prejudice to the subject matter of those claims, and are made merely in order to expedite prosecution of the application. Applicants expressly reserve the right to pursue the subject matter of those claims in this or a timely filed continuing application. The amendments to the claims should not be construed as conceding or acquiescing to the basis of any of the prior or pending rejections.

Further, the undersigned thanks Examiner Blanchard for the telephonic interview concerning the pending Office action. A separate response to the Interview Summary will be filed in due course.

# 2. Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 6, 8, 11, 13, 16, 18, 23, 25, 27, 29, 31-34, 38, 40, and 42-43 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing the enablement requirement. In particular the Office asserts that the specification fails to enable isolated human antibodies that comprise an "antigen-binding fragment thereof" of the recited heavy and/or light chain variable regions. The Patent Office asserts that while the claims were previously amended, the rejected claims "still only require three CDRs [from] either the heavy chain variable region or the light chain variable region...and as such do not require all six CDRs..." Applicants note that the Patent Office has provided a suggestion for amending

claim 59 and 65 to overcome the instant rejection, but have not included claims 59 and 65 in the instant rejection. Thus, Applicants assume that the Patent Office meant to include claims

59 and 65 in the instant rejection.

Merely in an effort to expedite prosecution of the application, Applicants have amended the claims (including claims 59 and 65), thereby obviating the rejection. Therefore,

Applicant respectfully request reconsideration and withdrawal of the rejection.

3. Rejections under 35 U.S.C. § 112, second paragraph

Claims 44-48 are rejected under 35 USC §112, second paragraph, asserted by the

Office to be indefinite for recitation of the phrases "The antibody of any of claims...wherein

the heavy chain and light chain are connected by a flexible linker to form a single chain antibody," or "which is a single chain Fv antibody," "which is a Fab antibody," "which is a

Fab' antibody," or "which is a (Fab')<sub>2</sub> antibody." Applicants have amended the claims in an

attempt to clarify the language, thereby obviating the rejection. Therefore, Applicant

respectfully request reconsideration and withdrawal of the rejection.

4. Conclusion

Date: March 10, 2009

Applicants respectfully contend that all conditions of patentability are met in the

pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited. If the Examiner has any concerns regarding this Response, he is

encouraged to contact the undersigned representative as indicated below at 312-913-0001.

Respectfully submitted,
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By: /Christopher P. Singer/

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